EXHIBIT G

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(54) Title: ORAL FORMULATION COMPRISING BIGUANIDE AND AN ORGANIC ACID

(57) Abstract

An oral formulation comprising a biguanide and an organic acid has less unpleasant tastes such as bitterness and saltiness.

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DESCRIPTION

ORAL FORMULATION COMPRISING BIGUANIDE AND AN ORGANIC ACID

TECHNICAL FIELD

The present invention relates to an oral fomulation comprising a biguanide and an organic acid.

BACKGROUND OF THE INVENTION

Biguanides such as metformin have unpleasant tastes such as bitterness and saltiness. The dosages of metformin are about 250 mg per dose in Japan and about 850 mg per dose in United States of America. In spite of such big dosages, only tablets are on sale at present.

There are several known methods for masking bitterness of bitter drugs, for instance, for solid formulations, sugar coated tablets, film coated tablets, capsules and the like are useful. Powders, fine granules and granules are formulated with sweetening agents or flavors; microcapsules, non-enteric coated formulation, spray-dried formulation with low melting point wax, formulation with lecithin (JP 62-265234-A) and the like may also be used. For solutions, there are formulations with water-insoluble high molecular weight compound such as ethylcellulose and hydroxypropylmethylcellulose phthalate (JP 52-41214-A); formulations with acidic phospholipids or lyso-phospholipids (JP 7-67552-A); and formulations with a large amount of citric acid (JP 4-58452-B).

DISCLOSURE OF THE INVENTION

The inventors of the present invention have intensively carried

out research, and found that an oral formulation comprising a biguanide and an organic acid has less unpleasant tastes such as bitterness and saltiness. Thus, the present invention has been accomplished.

The present inventions includes:

[1] An oral formulation comprising a biguanide and an organic acid.

[2] An oral formulation comprising a biguanide, an organic acid and a sweetening agent.

[3] An oral formulation according to [1] or [2] wherein the biguanide is metformin or a pharmaceutical salt thereof.

[4] An oral formulation according to any one of [1] to [3] wherein the organic acid is malic acid, citric acid, tartaric acid or mixture thereof.

[5] An oral formulation according to any one of [1] to [4] wherein the sweetening agent is aspartame™, saccharine, saccharine sodium, stevioside or mixture thereof.

[6] An oral formulation according to any one of [1] to [5] wherein the ratio (w/w) of the biguanide to the organic acid is 1 : 0.01 to 1 : 50.

[7] An oral formulation according to any one of [2] to [6] wherein the ratio (w/w) of the biguanide to the sweetening agent is 1 : 0.001 to 1 : 10

[8] An oral formulation according to any one of [1] to [7] wherein the formulation is solution, jelly, gum drops, dry syrup, powders, fine granules or granules.

[9] An oral formulation according to any one of [1] to [8] wherein the pH of the solution is 3.5 to 6 in case that the

formulation is solution, and the pH of the solution which is formed by dissolving or dispersing the formulation to 10 times more (w/w) volume of water, is 3.5 to 6 in case that the formulation is not solution.

DETAILED DESCRIPTION OF THE INVENTION

"Biguanide" includes compounds having a biguanide structure such as metformin, buformin, fenformin and pharmaceutically acceptable salts thereof.

"Organic acid" includes malic acid, citric acid, tartaric acid, ascorbic acid, succinic acid, fumaric acid, maleic acid, gluconic acid, glucuronic acid and mixtures thereof. Preferable organic acids are organic acids having 2 or 3 carboxyl groups such as malic acid, citric acid and tartaric acid, more preferably malic acid. The ratio (w/w) of the biguanide to the organic acid is, for example, 1 : 0.01 to 1 : 50, preferably 1 : 0.02 to 1 : 10, more preferably 1 : 0.05 to 1 : 1. In the case of malic acid, the preferable ratio (w/w) of the biguanide to malic acid is 1 : 0.05 to 1 : 0.5.

"Sweetening agent" includes aspartame™, saccharin, saccharin sodium, stevioside, *sormatin*, erythritol, sorbitol, xylitol, glycerin and mixtures thereof. Preferable sweetening agents are aspartame™, saccharin, saccharin sodium and stevioside. The ratio (w/w) of the biguanide to the sweetening agent is, for example, 1 : 0.001 to 1 : 10, preferably 1 : 0.02 to 1 : 1.

When the formulation is a solution, preferably the pH of the solution is 3.5 to 6, more preferably 4 to 6, to decrease the unpleasant tastes and to keep the biguanide stable. If the formulation is not a solution, the preferable pH of the solution or

dispersion which is formed by dispersing the formulation in water (1 part of the formulation to 10 parts of water, by weight), is 3.5 to 6, more preferably 4 to 6; This is in order to decrease the unpleasant tastes and to keep the biguanide stable.

"Oral formulation" includes solution, jelly, gum drops, dry syrup, powders, fine granules and granules. Preferably the formulation is not in the form of tablets.

The formulation of the present invention may include pharmaceutically acceptable non-toxic and inactive additives. Additives include excipients such as corn starch, potato starch, white sugar, mannitol, xylitol, sorbitol, talc, kaolin, calcium monohydrogen phosphate, calcium sulfate, calcium carbonate, crystalline cellulose; lubricants such as magnesium stearate and potassium stearate; disintegrators such as carboxymethylcellulose calcium and low substituted hydroxymethylcellulose; binders such as hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinypyrrolidone, gelatin, methylcellulose, Arabia gum and polyvinylalcohol; coloring agents; correctives; adsorbents; preservatives; stabilizers; moistening agents; de-charging agents; pH adjusters; and the like.

The formulation may include flavors such as lemon, orange, grapefruit, pine, banana, chocolate and yogurt to decrease the unpleasant tastes more.

The formulation of the present invention can be prepared by well known methods. In the case of solid formulations, the formulation can be prepared, for example, by extruding granulation

methods, crushing granulation methods, dry granulation methods, fluidized bed granulation methods, tumbling granulation methods, high shear mixing granulation methods, wet compression methods, direct compression methods and the like.

The formulation of the present invention will contain the conventional amounts of active ingredient (biguanide) and will be used in conventional manner to administer doses in accordance with normal practice by routes and according to dosage regimes which are familiar to pharmacologists and medical practitioners.

The present invention will be described in detail below, referring to Examples and Experiments, which are not limitative of the present invention.

Example 1

Solution of metformin hydrochloride

Ingredient	weight %
Metformin hydrochloride	5 %
Malic acid	0.8 %
Aspartame™	0.3 %
Lemon flavor	0.1 %
Purified water	93.8 %

5 % Solution of metformin hydrochloride is prepared by dissolving metformin hydrochloride, malic acid, aspartame™ and lemon flavor into purified water.

Example 2

Solution of metformin hydrochloride

Ingredient	weight %
Metformin hydrochloride	5 %
Malic acid	0.8 %
Saccharin sodium	1 %
Lemon flavor	0.1 %
Purified water	93.1 %

5 % Solution of metformin hydrochloride is prepared by dissolving metformin hydrochloride, malic acid, saccharine sodium and lemon flavor into purified water.

Example 3

Solution of metformin hydrochloride

Ingredient	weight %
Metformin hydrochloride	5 %
Citric acid	2 %
Aspartame™	0.3 %
Lemon flavor	0.1 %
Purified water	92.6 %

5 % Solution of metformin hydrochloride is prepared by dissolving metformin hydrochloride, citric acid, aspartame™ and lemon flavor into purified water.

Example 4

Solution of metformin hydrochloride

Ingredient	weight %

Metformin hydrochloride	5 %
Malic acid	1.5 %
Saccharin sodium	0.25 %
Erythritol	10 %
Lemon flavor	0.1 %
Purified water	83.15 %

5 % Solution of metformin hydrochloride is prepared by dissolving metformin hydrochloride, malic acid, saccharin sodium, erythritol and lemon flavor into purified water.

Example 5

Solution of metformin hydrochloride

Ingredient	weight %
Metformin hydrochloride	5 %
Malic acid	1.5 %
Aspartame™	0.2 %
Sorbitol	6 %
Grapefruit flavor	0.1 %
Purified water	87.2 %

5 % Solution of metformin hydrochloride is prepared by dissolving metformin hydrochloride, malic acid, aspartame™, sorbitol and grapefruit flavor into purified water.

Example 6

Solution of metformin hydrochloride

Ingredient	weight %
Metformin hydrochloride	5 %

Malic acid	1.5 %
Saccharin	0.03 %
Glycerin	10 %
Lemon flavor	0.1 %
Purified water	83.37 %

5 % Solution of metformin hydrochloride is prepared by dissolving metformin hydrochloride, malic acid, saccharin, glycerin and lemon flavor into purified water.

Example 7

Solution of metformin hydrochloride

Ingredient	weight %
Metformin hydrochloride	5 %
Malic acid	1.5 %
Saccharin sodium	0.25 %
Saccharin	0.03 %
Lemon flavor	0.1 %
Purified water	93.12 %

5 % Solution of metformin hydrochloride is prepared by dissolving metformin hydrochloride, malic acid, saccharin sodium, saccharin and lemon flavor into purified water.

Example 8

Dry syrup of metformin hydrochloride

Ingredient	Amount
Metformin hydrochloride	500 g
Malic acid	80 g

Saccharin sodium	25 g
Erythritol	865 g
Polyvinylpyrrolidone K30	30 g
Total	1500 g

Metformin hydrochloride, malic acid, saccharin sodium, erythritol and polyvinylpyrrolidone K30 are mixed with 200 g of mixture of purified water and ethanol (1 : 1 (w/w)) to give wet solid. 33 % Dry syrup of metformin hydrochloride is prepared by milling the wet solid with a granulation mill to adjust the size of the granules, followed by drying.

Example 9

Jelly of metformin hydrochloride

Ingredient	weight %
Metformin hydrochloride	5 %
Gelatin	0.5 %
Malic acid	0.8 %
Aspartame™	0.3 %
Lemon flavor	0.1 %
Purified water	93.3 %

Jelly of metformin hydrochloride is prepared by dissolving or dispersing metformin hydrochloride, malic acid, aspartame™ and lemon flavor into gelatin solution which is made by dissolving gelatin to purified water over 80 °C, followed by cooling.

Example 10

Fine granules of buformin hydrochloride

Ingredient	Amount
Buformin hydrochloride	100 g
Mannitol	300 g
Lactose	300 g
Corn starch	150 g
Malic acid	90 g
Aspartame™	30 g
Methylcellulose	30 g
Total	1000 g

Buformin hydrochloride, mannitol, lactose, corn starch, malic acid, aspartame™ and methylcellulose are mixed with 200 g of purified water to give wet solid. 10 % Fine granules of buformin hydrochloride are prepared by granulating the wet solid with a basket granulation mill, followed by drying.

Example 11

Gum drops of buformin hydrochloride

Ingredient	Amount
Buformin hydrochloride	100 mg
Gelatin	600 mg
Citic acid	100 mg
Saccharin sodium	25 mg
Sorbitol	1550 mg
Lemon flavor	25 mg
Purified water	600 mg

Total	3000 mg

Gum drops of buformin hydrochloride are prepared by dissolving or dispersing buformin hydrochloride, citric acid, saccharin sodium, sorbitol and lemon flavor into gelatin solution which is made by dissolving gelatin to purified water over 80 °C, followed by molding the mixture and cooling.

Example 12

Powders of buformin hydrochloride

Ingredient	Amount
Buformin hydrochloride	100 mg
Mannitol	560 mg
Corn starch	200 mg
Citric acid	100 mg
Aspartame™	30 mg
Magnesium stearate	10 mg
Total	1000 mg

10 % powders of buformin hydrochloride are prepared by mixing buformin hydrochloride, mannitol, corn starch, citric acid, aspartame™ and magnesium stearate.

Example 13

Solutions of metformin hydrochloride at various pH

Using the same amount of each ingredient of Example 1, 5 % solutions of metformin hydrochloride at various pH are prepared by dissolving or dispersing metformin hydrochloride, malic acid, aspartame™ and lemon flavor into about 80 % of purified water,

followed by adjusting pH of the solution to pH 2, 3, 3.5, 4, 5 or 6 using dilute hydrochloric acid or dilute sodium hydroxide solution and adding more purified water.

Reference example 1

Solution of metformin hydrochloride

Ingredient	weight %
Metformin hydrochloride	5 %
Purified water	95 %

5 % Solution of metformin hydrochloride is prepared by dissolving metformin hydrochloride into purified water.

Experiment 1

Tasting experiment

Tasting experiments on the solutions of Examples 1 to 3 and Reference example 1 were carried out with 20 panelists. The numbers of panelists who felt the solution "not bitter", "a little bitter" and "very bitter" are shown in Table 1.

Table 1

Solution	"not bitter"	"a little bitter"	"very bitter"
Example 1	11	8	1
Example 2	10	9	1
Example 3	11	8	1
Reference example 1	0	2	18

Tasting experiments on the solutions of Examples 4 to 7 were also carried out, with satisfactory results.

Experiment 2

Tasting and stability experiments

Tasting and stability experiments on the solutions at various pH of Example 13 were carried out, in the same manner as Experiment 1. A stability experiment was carried out by measuring the remaining amount of metformin in the solutions with HPLC after heating the solutions in vials at 60 °C for 2 weeks. The results are shown in Table 2.

Table 2

pH	taste	remaining amount(%)
2	very sour	78
3	sour	86
3.5	good	94
4	good	96
5	good	98
6	good	100
7	very bitter	98

Metformin hydrochloride is not stable below pH 3.5, and the solution tastes sour. The solution over pH 7 has bitterness.

Normally we feel bitterness most in solution formulation. Therefore these experiments on the solutions indicate that other formulations such as jelly, gum drops, dry syrup, powders, fine granules and granules have less unpleasant tastes as well.

The present invention provides an oral formulation of biguanide with less unpleasant tastes. With this invention, people in every age group, for example, elderly people and little children can easily have sufficient amount of biguanide.

CLAIMS

1. An oral formulation comprising a biguanide and an organic acid.

2. An oral formulation comprising a biguanide, an organic acid and a sweetening agent.

3. An oral formulation according to Claim 2 wherein the sweetening agent is selected from aspartame™, saccharine, saccharine sodium, stevioside and mixtures thereof.

4. An oral formulation according to Claim 2 or Claim 3 wherein the ratio (w/w) of the biguanide to the sweetening agent is 1 : 0.001 to 1 : 10

5. An oral formulation according to any one of Claims 1 to 4 wherein the biguanide is metformin or the pharmaceutical salt thereof.

6. An oral formulation according to any one of Claims 1 to 5 wherein the organic acid is selected from malic acid, citric acid, tartaric acid and mixtures thereof.

7. An oral formulation according to any one of Claims 1 to 6 wherein the ratio (w/w) of the biguanide to the organic acid is 1 : 0.01 to 1 : 50.

8. An oral formulation according to any one of Claims 1 to 7 in the form of a solution, jelly, gum drops, dry syrup, powders, fine granules or granules.

9. An oral formulation according to Claims 8 which is in the form of a solution wherein the pH of the solution is 3.5 to 6.

10. An oral formulation according to Claims 8 which is not in the form of a solution and the pH of the solution or dispersion which is formed by dispersing 1 part of the formulation in 10 parts

by weight of water is 3.5 to 6.

INTERNATIONAL SEARCH REPORT

Interr. ...nal Application No
PCT/JP 99/02192

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/155 A61K47/12 A61K47/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	GB 1 539 076 A (MEIJI SEIKA KAISHA) 24 January 1979 (1979-01-24) page 1, right-hand column, line 19-33 page 4; example 6 ---	1-10
Y	EP 0 390 369 A (AMERICAN HOME PROD) 3 October 1990 (1990-10-03) claims 1,2 ---	1-10
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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2 August 1999	13/08/1999

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	PATENT ABSTRACTS OF JAPAN vol. 010, no. 120 (C-343), 6 May 1986 (1986-05-06) & JP 60 246325 A (TAKEDA YAKUHIN KOGYO KK), 6 December 1985 (1985-12-06) abstract	1-10
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. nal Application No
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CLAIMS:

1. A liquid pharmaceutical composition for oral administration to a subject in need thereof which comprises a therapeutically effective amount of metformin or its pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable liquid carrier.

2. The liquid pharmaceutical composition according to claim 1, where the pharmaceutically acceptable carrier is water.

3. The liquid pharmaceutical composition according to claim 1 comprising a therapeutically effective amount of the pharmaceutically acceptable salt of metformin in association with a liquid carrier.

4. The liquid pharmaceutical composition according to claim 3, wherein the pharmaceutically acceptable salt is metformin hydrochloride.

5. The liquid pharmaceutical composition according to claim 3, wherein the pharmaceutically acceptable carrier is water.

6. The liquid pharmaceutical composition according to claim 1 which additionally comprises a sweetener that does not increase the blood glucose level of a subject after ingestion thereof.

7. The liquid pharmaceutical composition according to claim 1 which additionally comprises a sweetener that does not increase the blood glucose

level of a subject after ingestion thereof, an alkyl hydroxyethylcellulose, or a polyhydroxy alcohol, or combination thereof.

8. A liquid pharmaceutical composition which comprises a therapeutically effective amount of metformin, or its pharmaceutically acceptable salt, a sweetener that does not increase the blood glucose level of a subject after ingestion thereof, an alkyl hydroxyethylcellulose and a polyhydroxy alcohol in association with a pharmaceutically acceptable carrier, said sweetener being present in amounts ranging from about 40% to about 80% by weight, said alkyl hydroxyethylcellulose being present in amounts ranging from about 0.01% to about 5% by weight and said polyhydroxy alcohol being present in amounts ranging from about 5% to about 55% by weight.

9. The pharmaceutical composition of claim 8 wherein the sweetener is present in amounts ranging from about 50% to about 70% by weight.

10. The liquid pharmaceutical composition of claim 9, wherein the sweetener is present in amounts ranging from about 55% to about 65% by weight.

11. The liquid pharmaceutical composition of claim 8, wherein the alkyl hydroxyethylcellulose is present in amounts ranging from about 0.05% to about 1% by weight.

12. The liquid pharmaceutical composition of claim 11, wherein the alkyl hydroxyethylcellulose is present in amounts ranging from 0.08% to about 0.2% by weight.

13. The liquid pharmaceutical composition of claim 8, wherein the polyhydroxy alcohol is present in amounts ranging from about 15% to about 40% by weight.

14. The liquid pharmaceutical composition of claim 13, wherein the polyhydroxy alcohol is present in amounts ranging from about 20% to about 30% by weight.

15. The liquid pharmaceutical composition of claim 8, wherein the alkyl group in alkyl hydroxy ethyl cellulose contains 2 to 10 carbon atoms.

16. The liquid pharmaceutical composition of claim 8, wherein the sweetener is a sugar alcohol or non-nutritive sweetener.

17. The liquid pharmaceutical composition of claim 8, wherein the polyhydroxy alcohol contains 2 to 6 carbon atoms and contains 2 to 6 hydroxy groups

18. The liquid pharmaceutical composition of claim 8, wherein the polyhydroxy alcohol is a polymer having a molecular weight ranging from 200 to 2000 daltons and has a repeating unit of 2 to 6 carbon atoms and the repeating unit contains 2 to 6 hydroxy groups.

19. The liquid pharmaceutical composition according to claim 8, wherein the pharmaceutical carrier is water.

20. The liquid pharmaceutical composition according to claim 6 wherein the pH of the formulation ranges from about 4.0 to about 9.0.

21. The liquid pharmaceutical composition according to claim 20 wherein the sweetener is present in an amount ranging from about 10% to about 70%.

22. The liquid pharmaceutical composition according to claim 21 wherein the sweetener is a mixture of a sugar alcohol and a non-nutritive sweetener.

23. The liquid pharmaceutical composition according to claim 6 wherein the sweetener is a mixture of a sugar alcohol and a non-nutritive sweetener.

24. The liquid pharmaceutical composition according to claim 22 or 23 wherein the sugar alcohol is present in an amount ranging from about 10 to about 70% by weight and the nutritive sweetener is present in amounts ranging from about 0.1% to about 0.8% by weight.

25. The liquid pharmaceutical composition according to claim 22 or 23 wherein the sugar alcohol is xylitol.

26. The liquid pharmaceutical composition according to claim 22 or 23 wherein the non-nutritive sweetener is a saccharin salt.

27. The liquid pharmaceutical composition according to claim 22 or 23 which additionally comprises a mineral acid and a bicarbonate salt both in sufficient amounts to maintain the pH in the range of about 4.0 to about 9.0.

28. The liquid pharmaceutical composition according to claim 27 wherein the mineral acid is hydrochloric acid, nitric acid, or sulfuric acid.

29. The liquid pharmaceutical composition according to claim 28 wherein the mineral acid is hydrochloric acid.

30. The liquid pharmaceutical composition according to claim 20 wherein the pH ranges from about 4.2 to about 7.0.

31. The liquid pharmaceutical composition according to claim 27 wherein the bicarbonate salt is potassium bicarbonate.

32. A liquid pharmaceutical composition comprising a pharmaceutically effective amount of metformin or a salt thereof, a sweetening effective amount of a mixture of xylitol and saccharin or pharmaceutically acceptable salt thereof, and a mineral acid and bicarbonate salt, the acid and bicarbonate salt are present in an amount sufficient so that the pharmaceutical composition has a pH ranging from about 4.0 to about 9.0.

33. The liquid pharmaceutical composition according to claim 1, claim 8 or claim 22, in the form of a liquid suspension.

34. The liquid pharmaceutical composition according to claim 1 or claim 8 or 22 which additionally comprises an anti-hyperglycemic agent.

35. The liquid pharmaceutical composition according to claim 33, wherein the anti-hyperglycemic agent is glyburide or glypizide.

36. The liquid pharmaceutical composition according to claim 8, in the form of a liquid or a suspension comprising metformin hydrochloride, a non-nutritive sweetener, polyethylene glycol and alkyl hydroxyethylcellulose, wherein alkyl contains 2 to 12 carton atoms.

37. The liquid pharmaceutical composition according to claim 4, 32 or 36, additionally comprising an anti-hyperglycemic agent.

38. The liquid pharmaceutical composition according to any one of claim 1, 8 or 22 which additionally comprises a flavoring agent, an anti-oxidant, preservative, surfactant, thickener or a chelating agent.

39. The liquid pharmaceutical composition according to claim 38 which additionally comprises an anti-hyperglycemic agent.

40. A method of treating diabetes in a subject in need of treatment comprising administering to said subject an anti-diabetic effective amount of the liquid pharmaceutical composition of any one of claims 1, 8 or 22.

41. A method of treating hyperglycemia in a subject suffering therefrom which comprises administering to said subject an anti-hyperglycemic effective amount of the liquid pharmaceutical composition of any one of claims 1, 8 or 22.

42. A method for reducing adverse effects of metformin or its pharmaceutically acceptable salt when ingested, which comprises administering to a patient a liquid pharmaceutical composition of any one of claims 1, 8 or 22.

43. A method for facilitating compliance of a patient prescribed to take metformin or its pharmaceutically acceptable salt which comprises administering thereto a pharmaceutically effective amount of the liquid pharmaceutical composition of any one of claims 1, 8 or 22.

44. The liquid pharmaceutical composition according to claim 8 wherein the polyhydric alcohol is a mixture of a first polyethylene glycol having a molecule weight between 200 and 1000 daltons inclusive and a second polyethylene glycol having a molecular weight between 1000 and 2000 dalton, inclusive.

45. The liquid pharmaceutical composition according to claim 44 wherein the weight ratio of the first polyethylene glycol to the second polyethylene glycol ranges from about 1.5:1 to about 4:1.

46. The liquid pharmaceutical composition according to claim 21 wherein the sweetener is present in amounts ranging from about 20% to about 60% by weight.

47. The liquid pharmaceutical composition according to claim 46 wherein the sweetener is present in amounts ranging from about 30% to about 50% by weight.

48. The liquid composition according to claim 24 wherein the weight ratio of sugar alcohol to non-nutritive sweetener ranges from about 700:1 to about 85:1.

49. The liquid composition according to claim 48 wherein the weight ratio of sugar alcohol to non-nutritive sweetener ranges from about 300:1 to about 100:1.

50. The liquid composition according to claim 48 wherein the weight ratio of sugar alcohol to non-nutritive sweetener ranges from about 200:1 to about 110:1.